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CLINICAL PRACTICE

Update in Women's Health for the General Internist

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This clinical update summarizes articles and guidelines published in the last year that may impact general internists' clinical practice related to women's health.

METHODS

To identify relevant articles published between March 1, 2009 and February 28, 2010, we reviewed the contents of leading medical journals including: the New England Journal of Medicine, the Journal of the American Medical Association, Annals of Internal Medicine, Archives of Internal Medicine, British Medical Journal, Lancet, Obstetrics and Gynecology, American Journal of Obstetrics and Gynecology, Journal of General Internal Medicine, PLOSMedicine, American Journal of Public Health, Circulation, Diabetes, and Diabetes Care. We also reviewed updates to the Cochrane database of systematic reviews, Guideline Clearinghouse, and the articles highlighted by the ACP Journal Club, Journal Watch and Journal Watch Women's Health. Finally, we performed a MEDLINE search using the medical subject heading, "sex factors." Those abstracts rated in the top third of importance by any author were read closely and rated by all authors. A process of individual ratings and multiple discussions was then used to reach consensus about the most important articles published in the last year.

RESULTS

We identified 152 articles relevant to women's health; 20 articles were selected for presentation at the annual meeting and 12 for detailed discussion in this paper.

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MIGRAINE AND CARDIOVASCULAR RISK

Migraine and Cardiovascular Disease: Systemic Review and Meta-Analysis[1]

What was known?. Migraines affect up to 13% of the population and are significantly more common in women. Up to a third of migraine patients experience aura. A 2004 meta-analysis showed a significant association between ischemic stroke and both migraine with and without aura.[2]

What this study adds. This updated meta-analysis incorporates data from six new studies, including three large cohort studies (which increased the sample size from roughly 7800 patients to over 210,000 patients). Only well-designed case-control or cohort studies were included. The investigators found that migraine with aura was associated with a two-fold increase in risk for ischemic stroke (RR=2.16, 95%CI, 1.53-3.03). The risk was higher for women than men (RR=2.08, 95%CI, 1.13-3.84), those<45 years (RR=2.65, 95%CI, 1.41-4.97), smokers (RR=9.03, 95%CI, 4.22-19.34), and oral contraceptive users (RR=7.02, 95%CI, 1.51-32.68). Patients with migraine without aura showed no increased risk. There was no association between migraine and myocardial infarction or cardiovascular death.

How should I change my practice?. Aggressive modification of cardiovascular risk factors and alternatives to estrogen-containing contraceptives should be considered for women with migraine with aura.

OVARIAN CANCER SCREENING

Results from Four Rounds of Ovarian Cancer Screening in a Randomized Trial[3]

What was known?. Annually in the United States, over 22,000 women are diagnosed with ovarian cancer and over 15,000 die from the disease. Prognosis is greatly improved with diagnosis at an early stage (Stage I or II) compared with later stages. To date, attempts to screen for ovarian cancer

using either transvaginal ultrasound or CA125 tumor marker levels have not reduced mortality.[4,5]

What this study adds. This study examined whether screening with both transvaginal ultrasound and CA125 would reduce mortality from ovarian cancer. Over 34,000 women aged 55-74 years were randomized to annual transvaginal ultrasound and CA125 vs. usual care for four years. If either was positive, management was per the patient's personal physician. At the baseline screen, 5.8% of women were positive for either test, 33.8% of whom (n=566) underwent biopsy, resulting in the diagnosis of 18 new ovarian cancers (83% were Stage III or IV). By the end of the 4th round of screening, 42 additional invasive cancers were diagnosed (67% late stage). With each round of screening, the number of cancers diagnosed per 10,000 women screened ranged from 4.7-5.9. The ratio of surgery to invasive cancer was 31:1 at the baseline screen and decreased to 14:1 by the end of round 4. Cases detected by ultrasound only (normal CA125) tended to be early stage (71% of 14 cases), but these drove most of the unnecessary surgeries. Cases detected by elevated CA125 (regardless of ultrasound) predicted late stage (79-89%).

How should I change my practice?. This study reinforces current USPSTF guidelines[6] that screening for ovarian cancer is not recommended with annual transvaginal ultrasound or CA125 in women of average risk. It remains to be seen whether screening will impact mortality.

BREAST CANCER RISK

New Onset Breast Tenderness After Initiation of Estrogen Plus Progestin Therapy and Breast Cancer Risk[7]

What was known?. Combination postmenopausal hormone therapy (PHT) has been associated with a 30% increase in breast cancer risk in the Women's Health Initiative (WHI) Trial.[8] Of women who initiate PHT, up to 25% develop new-onset breast tenderness (NOBT), perhaps linked to increased breast cell proliferation. This NOBT has been associated with increased mammographic density,[9] and mammographic density is a risk factor for breast cancer.[10] Thus, it is biologically plausible that NOBT could be associated with breast cancer incidence.

What this study adds. These investigators sought to determine if NOBT with initiation of PHT is predictive of breast cancer development using data from the WHI trial, in which 16,608 women were randomized to conjugated equine estrogens+medroxyprogesterone acetate vs. placebo. Baseline and annual breast exams and mammograms were performed. Breast tenderness was assessed by a four-point Likert scale at baseline and 1st annual follow-up. After a mean follow-up of 5.6 years, 36.1% of women taking PHT developed NOBT vs. 11.8% of women taking placebo (RR= 3.07, 95%CI, 2.85-3.30). In the PHT group, the risk of breast cancer was higher in women with NOBT (HR=1.48, 95%CI, 1.08–2.03). There was no association in the placebo group.

How should I change my practice?. Information about whether a woman develops NOBT can inform decision-making about continuation of PHT and mammographic screening intervals. The symptom is easy to elicit and has a positive predictive value (2.7%) that is similar to the Gail model. Although women taking PHT who develop NOBT have an increased risk of invasive breast cancer, the absolute risk remains small.

BREAST CANCER SCREENING

Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force[11]

What was known?. Breast cancer accounts for almost 1 in 4 cancers in U.S. women, and screening mammography reduces breast cancer mortality.[12,13] However, when to start screening mammography remains controversial. A systematic review and meta-analysis conducted in 2002 showed a 15% relative risk reduction among women aged 40-49;[14] however, only one of the included trials was specifically designed to address this issue. Additionally, the analysis did not provide a comprehensive review of the harms associated with screening mammography. Questions also remained about the effectiveness of mammography in older women, and the utility of clinical and self breast exams.

What these studies add. The United States Preventive Services Task Force updated the 2002 meta-analysis regarding mammography benefit in women aged 40-49 to include two new sources of data. Pooling these data with those from the previous meta-analysis resulted in a 15% relative risk reduction (95%CI 0.75-0.96) in breast cancer mortality among women aged 40-49 years. However, this was balanced with a high number needed to invite to prevent one breast cancer death (1904: 95%CI 929-6378) and a high false positive rate in this age group (97.8 per 1000 screened). Evidence was insufficient regarding the benefits of mammography in women older than 70 and the clinical breast exam; breast self-exam did not have any net benefit. A model of the effectiveness of various mammographic screening strategies for reducing breast cancer mortality[15] found that the most efficient models initiated screening at age 50 with a biennial interval. Starting screening at age 40 reduced breast cancer mortality by an additional 3% but resulted in more false-positives, whereas biennial screening over the age of 50 retained 81% of the benefit achieved with annual screening.

How should I change my practice?. Screening mammography for women aged 40-49 should not be reflexive. Biennial screening retains the same benefits as annual screening and

should be recommended for women over 50 years. The benefits of clinical breast exam, and of mammography in women over 70 years, remain inconclusive.

PRIMARY CARE FOR WOMEN WITH BREAST CANCER

Selective Serotonin Reuptake Inhibitors and Breast Cancer Mortality in Women Receiving Tamoxifen: A Population-Based Cohort Study[16]

What was known?. Tamoxifen is a selective estrogen receptor modulator used to treat breast cancer.[17] The cytochrome P450 isoenzyme CYP2D6 catalyzes the conversion of tamoxifen to its bioactive metabolite, endoxifen.[18] Paroxetine is a potent inhibitor of the CYP2D6 isoenzyme, which lowers serum concentrations of endoxifen;[18] co-administration of these medications may have clinical consequences.

What this study adds. This retrospective cohort study examined the prescription and clinical records of 2,430 older women with breast cancer who received simultaneous treatment with tamoxifen and a single selective serotonin receptor inhibitor (SSRI). Using within-drug comparisons, the investigators examined associations between breast cancer death and co-treatment time with tamoxifen and an SSRI. For women treated simultaneously with tamoxifen and paroxetine, increases of 25%, 50%, and 75% in the proportion of time that paroxetine and tamoxifen treatment overlapped resulted in increased risk of breast cancer death of adjusted HR=1.24 (95%CI 1.08-1.42), 1.54 (95%CI 1.17-2.03) and 1.91 (95%CI 1.26-2.89), respectively. Similar associations were not noted for co-treatment with any other antidepressants; hazard ratios were actually lower with increasing co-treatment time with venlafaxine and tamoxifen

How should I change my practice?. Practitioners should avoid prescribing paroxetine to women treated with tamoxifen.

Soy Food Intake and Breast Cancer Survival[19]

What was known?. Soy foods are rich in isoflavones, which have both estrogen and anti-estrogen effects.[20] Controversy exists regarding the effects of soy consumption on breast cancer risk.[20,21]

What this study adds. This large, prospective cohort study, involving 5,042 breast cancer survivors in Shanghai, assessed the association between soy food intake and total mortality, breast cancer mortality, and breast cancer recurrence. Soy food and isoflavone intake were measured 18 months, 36 months, and 60 months after breast cancer diagnosis and were grouped by quartiles. When comparing the lowest intake quartile to the highest, increasing soy protein intake was associated with a decreased risk for total mortality (adjusted HR=0.71, 95%CI 0.54-0.94) and breast cancer recurrence and mortality (adjusted HR=0.68, 95%CI 0.54-0.87). Similar effects were noted in women with ER-positive breast cancer, although all confidence intervals crossed 1.0. In addition, tamoxifen use seemed to improve survival only among women with low-moderate soy food intake, although this result was not statistically significant.

How should I change my practice?. There is no need to counsel breast cancer patients to avoid soy-containing foods and beverages. The average amount of soy protein consumed by participants in this study was 47 mg/day, which far exceeds the average 1-6 mg/day consumed by American women. The study resulted in new cancer screening guidelines (Table 1).

OSTEOPOROSIS

Vitamin D and Fractures

Prevention of Nonvertebral Fractures with Oral Vitamin D and Dose Dependency: Meta-Analysis of Randomized Controlled Trials[22]

What was known?. Vitamin D deficiency is common in older adults, homebound individuals and women admitted with hip fracture. The association between vitamin D levels and fracture risk has been inconsistent, although a recent well done case-control study showed that women with lower serum 25-OH-vitamin D levels had a higher fracture risk than women with higher levels and there was a dose response effect.[23] Although women are frequently treated for vitamin D deficiency, it has not been known whether vitamin D supplementation prevents non-vertebral and hip fractures.

What this study adds. This well-done meta-analysis included twelve studies that evaluated vitamin D supplementation and reported at least one fracture. Studies had to be double-blind with at least one year of follow-up and data on adherence. Participants took either cholecalciferol (D_3) or ergocalciferol (D_2). Vitamin D doses >400 IU per day reduced nonvertebral and hip fractures but lower doses did not. The overall reduction was relatively small (RR=0.86, 95%CI 0.77-0.96) for nonvertebral fractures. The addition of calcium did not enhance the effect of Vitamin D. In addition, the anti-fracture efficacy was higher with higher achieved 25-OH vitamin D levels.

How should I change my practice?. Recommendations for vitamin D supplementation have typically targeted the goal of achieving a particular 25-OH-vitamin D level, rather than a clinical outcome. We now know that vitamin D supplementation can reduce fracture risk and should be considered for women with osteoporosis and potentially osteopenia. Further study is needed to clarify when supplementation should begin and whether there is added value to co-treatment with calcium and/or bisphosphonates.

Table 1. Important Women's Health Guidelines in 2009-2010: New or Updated

Topic	Issuing organization	Updated recommendations
Cervical Cancer Screening	ACOG	Cervical cancer screening should begin at age 21 regardless of the age of onset of sexual activity Screening should occur every 2 years in women aged 21-29 (more frequently in women with HIV, immunosuppression, DES exposure of history of CIN) Women aged 30 and over who have had at least 3 negative smears can be screened every 3 years (Co-testing with cervical cytology and high risk HPV typing is also appropriate; if co-testing is negative, rescreening can occur in 3 years) Women who have had a hysterectomy do not need cervical cancer screening After age 65-70, screening can cease in women who have had at least 3 previous negative tests and no abnormalities in the past 10 years Those with CIN2, CIN3 or cancer should undergo annual screening for 20 years HPV vaccine does not change these recommendations
Breast Cancer Screening	USPSTF	The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms[51,52] Screening mammography is recommended every two years for all women aged 50 to 74 There is insufficient evidence to weight the benefits and harms of screening mammography for women older than 75 The evidence for the clinical breast exam is insufficient; women should not be taught how to do breast self-exam

ACOG American College of Obstetrics and Gynecology
CIN cervical intraepithelial neoplasia
HPV human papilloma virus
USPSTF United States Preventive Task Force

BONE MINERAL DENSITY MONITORING

Value of Routine Monitoring of Bone Mineral Density After Starting Bisphosphonate Treatment: Secondary Analysis of Trial Data[24]

What was known?. Screening bone densitometry is recommended for women aged 65 and over as well as for younger women with risk factors,[25] however whether bone mineral density (BMD) should be monitored once treatment is started is controversial.[26-28]

What this study adds. This study was a reanalysis of data from the Fracture Intervention Trial (FIT),[29] in which women were treated with alendronate or placebo, received annual bone densitometry and were followed for fractures. Investigators compared "within- person" variation (measurement) with "between-person" variation (treatment effect) in serial bone density measurements. They found that within-person measurement-related variation was greater than between-person treatment- related variation, suggesting that routine monitoring of BMD during the first three years of bisphosphonate treatment is unnecessary. The vast majority of individuals (97.5%) gained bone mineral density with alendronate treatment.

How should I change my practice?. Monitoring BMD in postmenopausal women after starting bisphosphonate treatment for osteoporosis is not necessary. Treatment "failure" is best described by fracture while on therapy rather than a decrease in BMD.

TREATMENT OF OSTEOPOROTIC COMPRESSION FRACTURES

Efficacy and Safety of Balloon Kyphoplasty Compared with Non-Surgical Care for Vertebral Compression Fracture (Free): A Randomized Contolled Trial[30]

What was known?. Spontaneous vertebral fractures can cause significant morbidity and mortality. The use of both vertebroplasty (augmentation of vertebral compression fractures with polymethylmethacrylate (PMAA)) and kyphoplasty (inflating a balloon to restore the vertebral body to its original height while creating a cavity into which PMMA can be injected under low pressure) is increasing despite little evidence to support their use[31]. There have also been reports of procedures being repeated at previously treated levels and the use of prophylactic vertebroplasty at levels deemed to be at high risk for fracture[32,33]

What this study adds. Kyphoplasty was compared to nonsurgical care in 300 participants in 18 countries in participants with acute vertebral fractures of less than 3 months duration. Nonsurgical care included back brace, walking aids, analgesics and physical therapy. At one month follow-up, kyphoplasty recipients had significant improvement in the SF-36 physical component, 5.2 points (95%CI 2.9-7.4) greater than those who received nonsurgical care. At 12 months, there were no differences in outcomes between groups, and subsequent fractures were common in both groups (33% vs 25% control p=NS).

How should I change my practice?. In patients with acute fractures, kyphoplasty improves pain and function at 1 month,

but after 12 months, there was no difference compared with usual care. Kyphoplasty appears to be safe in the short term. Of note, two recent trials showed no benefit of vertebroplasty compared with placebo, although there was a high rate of crossover in the studies; it is possible that the placebo injected into the periosteum may have had some analgesic effect and the participants had fractures that were less acute (<12 months in duration). For individuals with compression fractures who have failed conservative treatment, kyphoplasty may be an option to improve symptoms at one month. Longer term data on efficacy are needed.

LACTATION AND MATERNAL HEALTH

Duration of Lactation and Incidence of the Metabolic Syndrome in Women of Reproductive Age According to Gestational Diabetes Mellitus Status: A 20-Year Prospective Study in CARDIA[34]

What was known?. Retrospective studies have shown that lactation decreases a mother's risk of developing hypertension,[35] hyperlipidemia,[35] diabetes mellitus,[36,37] and cardiovascular disease.[38,39] Although major US medical organizations recommend women breastfeed each of their children for at least 12 months,[40-42] only 24% of US women are able to comply with this recommendation.[43]

What this study adds. This prospective cohort study included 1399 nulliparous women, aged 18-30, who had no evidence of metabolic syndrome on blood tests or blood pressure measurements performed at the time of study enrollment. Over twenty years of follow up, 704 women reported one or more singleton births and 120 developed the metabolic syndrome. In analyses controlling for age, race, education, parity, smoking, physical activity, baseline BMI and components of metabolic syndrome, this study found that mothers who did not lactate were at greater risk of developing the metabolic syndrome. These findings were particularly striking for women who had developed gestational diabetes mellitus(GDM); those who lactated for less than 1 month were much more likely to develop the metabolic syndrome (HR=7.14, 1.82-25.00) than mothers who lactated for more than 9 months after a pregnancy affected by GDM. Among mothers who did not lactate incident metabolic syndrome was more common among pregnancies affected by GDM (49.4 per 1000 person-years) than those not affected by GDM (16.7 per 1000 person-years). In contrast, among mothers who breastfed for more than 9 months, those with GDM (8.5 per 1000 person years) were not more likely than those without GDM (9.2 per 1000 person years) to develop the metabolic syndrome.

How should this change my practice?. Women who discontinue lactation before nine months postpartum are at increased risk of developing the metabolic syndrome and may benefit from more aggressive lifestyle modification and screening for cardiovascular disease. Breastfeeding mothers should be encouraged and women considering pregnancy should be informed that breastfeeding has important effects on both maternal and infant health.

CONTRACEPTION

Hormonal Contraception and Risk of Venous Thromboembolism: National Follow-Up Study[44]

What was known?. Estrogen-containing contraceptives increase risk of venous thromboembolism (VTE). Concern had been raised that some progestins may also increase risk of VTE.[45]

What this study adds. This national cohort study followed Danish women, aged 15-49, from 1995 to 2005. Using data from 4 linked databases, the investigators identified 4,213 first-time VTE over 10.4 million woman-years of observation. The authors report the absolute risk of VTE in young women using oral contraceptives is less than one per 1000 user-years. In addition, the authors found that women using progestin-only pills (adjusted RR=0.59, 95%CI 0.33-1.04) or the levonorgestrel-containing intrauterine contraceptive (aRR=0.89, 95%CI 0.64-1.26) were no more likely to develop VTE than non-users of oral contraceptives. However, women using estrogen containing contraceptives were two to four times as likely as non-oral contraceptive users to develop VTE. In models adjusted for women's age, educational level, length of use, and calendar year, combined oral contraceptives that contained desogestrel (aRR=1.82, 1.49-2.22), gestodene (aRR=1.86, 1.59-2.18), or drospirenone (aRR=1.64, 1.27-2.10) were more frequently associated with VTE than oral contraceptives containing the progestin levonorgestrel.

How should this change my practice?. All women seeking contraception, and especially those at increased risk of VTE, should be encouraged to consider highly effective reversible options that are estrogen-free such as an intrauterine contraceptive or a contraceptive implant; those women who prefer to use a combined oral contraceptive should be offered a product containing levonorgestrel, norethindrone, or norgestimate as first line options.

Ulipristal Acetate Versus Levonorgestrel for Emergency Contraception: A Randomised Non-Inferiority Trial and Meta-Analysis[46]

What was known?. Levonorgestrel emergency contraception pills (ECP), which are available in the US without a prescription to all individuals over the age of 17 as Plan B one step or the generic, Next Choice, are at least twice as effective as the Yuzpe regimen.[47,48] However, as unintended pregnancy and abortion remain common,[49] the search for better contraceptives continues.

What this study adds. This randomized, blinded, controlled trial, which enrolled 2221 women from 35 clinics in the United Kingdom, Ireland, and the USA, was designed to show that 30 mg of ulipristal acetate is non-inferior to 1.5 mg of levonorgestrel when used as EC within 5 days of unprotected intercourse. Adverse events were similar between groups and included headache (19%), dysmenorrhea (14%), and nausea (12%). Pregnancy rates with use of either ECP (1.8% with ulipristal acetate vs 2.6% with levonorgestrel) were lower than the 5.5 % expected without use of ECP. In a meta-analysis which combined the results of this study with a similar study,[50] the investigators reported that women using ulipristal acetate for EC were less likely than women using levonorgestrel within 5 days of unprotected sex to become pregnant (OR=0.55, 95%CI 0.32-0.93).

How should this change my practice?. Ulipristal acetate has recently been approved for EC use in Europe and the US (as "ella"). Advance prescription of ulipristal acetate should be considered for all patients using barrier methods of contraception.

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